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BETHANY L. LACLAIR

Evaluation of the Risk Factors for Antibiotic Resistance in *Streptococcus Pneumoniae*

Cases in Georgia

(Under the direction of Dr. Lisa Casanova)

Introduction: *Streptococcus pneumoniae* is the main bacterial cause of pneumonia, bacteremia and meningitis. Incidence rates have decreased since the initiation of pneumococcal vaccines, but antibiotic resistant strains continue to emerge and place a heavy burden on healthcare systems to treat such serious resistant infections. This study looks at risk factors that increase a patients probability of contracting a drug resistant strain of *S. pneumo*.

Methods: Confirmed cases of *S. pneumo* were acquired through the Active Bacterial Core Surveillance program from 2009-2012 for the state of Georgia. Cumulative incidence rates, odds ratios and Pearson's chi square were calculated to test for trends. Multi-logistic regression model was designed to control for covariates. Antibiotic Susceptibility results were analyzed by resistant profiles through WHONET.

Results: Cumulative incidence rates have decreased significantly, however antibiotic resistant and multidrug resistant strains have increased. Incidence rates for children less than five and adults over 65 have decreased, however, the burden of disease remains in young to middle adults. Antibiotic resistant strains have shifted from penicillin to erythromycin and cefotaxime.

Discussion: Interventions need to be targeted towards young to middle aged adults. Antibiotic stewardship programs should seek uniform guidelines to battle the increasing emergence of multidrug resistant strains.

INDEX WORDS: antibiotic resistance, streptococcus pneumoniae, Georgia, antibiotic stewardship

EVALUATION OF THE RISK FACTORS FOR ANTIBIOTIC RESISTANCE IN
STREPTOCOCCUS PNEUMONIAE CASES IN GEORGIA

by

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B.A., MERCER UNIVERSITY

A Thesis Submitted to the Graduate Faculty of Georgia State University in Partial Fulfillment of
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MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

30303

APPROVAL PAGE

EVALUATION OF THE RISK FACTORS FOR ANTIBIOTIC RESISTANCE OF
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CHAPTER I—INTRODUCTION

Streptococcus pneumoniae, also abbreviated as *S. pneumo*, is a gram-positive bacterium and commonly found in the upper respiratory tract of health humans (McGraw-Hill, 2007). Currently, there are 90 different serotypes of *S. pneumo*, which are differentiated by its capsular polysaccharide (McGraw-Hill, 2007). The various serotypes of *S. pneumo* are the major bacterial cause of invasive disease such as pneumonia, meningitis and bacteremia (Heymann, 2008). There are other non-invasive infections that *S. pneumo* causes such as otitis media in children (McGraw-Hill, 2007; Whitney et. al., 200). Typically, the main source of transmission for invasive pneumococcal disease (IPD) is from children to household contacts and adults (Heymann, 2008; Lynch & Zhanel, 2010). IPD occurs when pneumococcus enters sites of the body other than the respiratory tract such as blood, pleural fluid or central spinal fluid (CSF) (Heymann, 2008; Cornick & Bentley, 2012).

Penicillin has been the standard of care for invasive *S. pneumo* infections (Heymann, 2008; Cornick & Bentley, 2012). However, the Control of Communicable Diseases Manual outlines other alternative antibiotic treatments for IPD to clinicians for those who may be penicillin resistant. For the treatment of pneumococcal meningitis, the recommended antibiotic regimen is penicillin or cefotaxime (Heymann, 2008). However, for patients with sensitivity to penicillin, cefotaxime with vancomycin is recommended for empirical treatment until antibiotic susceptibility results are confirmed (Heymann, 2008). For pneumococcal pneumonia, penicillin or amoxicillin are preferred treatment regimens (Heymann, 2008). If a patient is sensitive to penicillin, erythromycin is recommended (Heymann, 2008). For patients diagnosed with

bacteremia, the Infectious Disease Society of America recommends clinicians use combination therapy of a β -Lactam plus a macrolide or fluoroquinolone (File & Mandell, 2003).

As previously described, *Streptococcus pneumoniae* causes severe illness in those infected and places a large burden on the population and the healthcare system. Georgia is a participating site in the Active Bacterial Core Surveillance (ABCs) program conducted through the Emerging Infections Program by the Centers for Disease Control and Prevention. The ABCs program conducts active and passive surveillance on various invasive bacterial diseases to control and understand the characteristics of such diseases in the population. ABCs confirmed cases are reported directly to the state by hospitals, laboratories or found by the state through location audits. Many of the isolates from the patients are sent to local laboratories to obtain serotyping and antibiotic susceptibility testing. In addition, medical charts for each patient are requested by the state to gather information on risk factors such as demographics, diagnosis, vaccine history and underlying conditions. One of the five pathogens the ABCs program monitors is *Streptococcus pneumoniae*.

Antibiotic resistant strains increase severity of illness and make it more difficult to effectively treat infections. The following analysis will examine the relationship between risk factors, such as age, race location and diagnosis, and the presence of antibiotic resistant *S. pneumo*. Results from this study will help clinicians to understand the severity of the problem, how the pneumococcal vaccines have affected the incidence of *S. pneumo* cases and encourage innovative public health interventions through antibiotic stewardship programs.

CHAPTER TWO—LITERATURE REVIEW

Epidemiology of Streptococcus Pneumoniae

It is estimated that 1.6 million people, including 1 million children worldwide will die annually from invasive pneumococcal disease (IPD) (Lynch & Zhanel, 2010). A review of the literature found that mortality rates for bacteremia and pneumonia caused by *S. pneumo* is 10-30% in adults and less than 3% in children worldwide (Lynch & Zhanel, 2010). For meningitis, mortality rates are 16-37% for adults and 1-3% for children worldwide.

The Prospective Resistance Organism Tracking and Epidemiology for the Ketolide Telithromycin in the US (PROTEKT US) is a surveillance study on *S. pneumo* and other respiratory tract infections from 2000-2004 (Jenkins, Brown & Farrell, 2008). Over the four year surveillance period, an average of 27% of the cases were less than five years old, 42% were between 15-64 years old and 29% were 65 and older (Jenkins et. al., 2008). This study also discovered that nearly 50% of all cases were hospitalized, which places a large burden on the United States Healthcare system.

Other studies found similar rates based on age, For example, the Active Bacterial Core Surveillance program through the CDC disseminated their 2010 annual report providing epidemiologic statistics on *S. pneumo* in the United States. Provided below is a table describing the incidence and mortality rates by age group:

Table 1: Incidence and Mortality Rates for Streptococcus Pneumoniae in 2010 (CDC)

Age (years)	Cases No. (Rate*)	Deaths No. (Rate*)
<1	142 (34.2)	1 (0.24)
1	112 (26.6)	1 (0.24)
2-4	171 (13.1)	1 (0.08)
5-17	111 (2.2)	1 (0.02)
18-34	260 (3.8)	18 (0.26)
35-49	670 (10.5)	43 (0.68)
50-64	1,064 (18.8)	104 (1.84)
≥ 65	1,292 (36.4)	200 (5.63)
Total	3,822 (12.8)	369 (1.24)

*Cases or deaths per 100,000 population for ABCs areas

The incidence rate in 2010 among whites was 12.2/100,000 and blacks was 17.6/100,000 (Active Bacterial Core Surveillance Report). The ABCs report also included information about disease outcome and found 70.3% of cases were diagnosed with pneumonia, 16.8% with bacteremia, and 6.0% with meningitis (ABC Report). Limited recent research studies have specifically focused their research in the state of Georgia. Dr. Hofman and colleagues conducted a study in Atlanta in 1998 to understand the burden of drug resistant *S. pneumo* in the Atlanta area (1995). The study found an incidence rate of 30 cases per 100,000 individuals and 6 cases per 100,000 of penicillin resistant *S. pneumo* (Hofmann et. al, 1995). However, their study only consisted of the 20 metro-Atlanta counties (Hofmann et. al, 1995). Currently, there is no research on the burden of *S. pneumo* on the entire 159 counties in Georgia.

In 1998, Dr. Cynthia Whitney and colleagues examined the risk factors for antibiotic resistant *S. pneumo* in the United States (Whitney et. al., 2008). The study population consisted of patient diagnosed in 1995-1998 with invasive pneumococcal disease in eight ABC locations: Oregon, California, New York, Minneapolis, Baltimore, Atlanta, Tennessee and Connecticut (Whitney et. al., 2008). Dr. Whitney found an increase in multi-drug resistant *S. pneumo*

infections based on several risk factors such as age, race, location and hospitalization. She concluded a strong association between these risk factors and a patient acquiring a multidrug resistant strain of *S. pneumo* (Whitney et. al., 2008). Among the sites included in the study population, Georgia had the highest number of cases of *S. pneumo* (726) and the second highest number of penicillin resistant isolates (33.2%) (Whitney et. al., 2008). Again, the study population in Georgia only included the 20 metro-Atlanta counties (Whitney et. al., 2008). The analysis performed by Dr. Whitney and associates will be used as a model for the following research conducted on the whole state of Georgia.

Risk Factors for Streptococcus pneumoniae

The PROTEKT study between 2000 and 2004 examined drug resistant *S. pneumo* (DRSP) from varying geographic regions across the United States (Jenkins et. al., 2008). Dr. Jenkins and his associates discovered geographic variations among DRSP cases with the Southeast having one of the highest number of DRSP cases in comparison to other regions such as the Northeast and South-central (Jenkins et. al., 2008). The Southeast had 1025 penicillin resistant isolates which is 19.1% of all isolates compared to 10% in other regions (Jenkins et. al., 2008). Therefore, geographic location could be a risk for a potential increase in DRSP cases. In addition, another study conducted in 2006 by Dr. Draghi and associates examined the geographic variations among multidrug resistant strains of *S. pneumo* (2006). The results found striking variations between regions in the US with penicillin resistant strains as low as 7.5% in New York and nearly four times higher in Phoenix with 29.4% of isolates (Draghi, Jones, Sahm & Tilletson, 2006). Also, multidrug resistant strains varied as well with 18.8% in Denver and over 40% in Florida (Draghi et. al., 2006). Therefore, this study is synonymous with previous studies and demonstrates variation between geographic regions as a potential risk factor for DRSP.

Dr. Hofman's study on DRSP in Atlanta found a statistically significant association between race and *S. pneumo* infections. In 1994, the incidence rate for blacks with *S. pneumo* in Atlanta was 58 per 100,000; while whites were 18 per 100,000 individuals (Hofmann et. al, 1995). In conjunction with location as a risk factor, Dr. Hofman describes race and location may be a proxy for socioeconomic status and access to health care and therefore blacks are at a greater risk for DRSP (Hofmann et. al, 1995). Even with a greater number of cases among blacks, alternatively, the study also determined white children under the age of six are at a higher rate of disease (Hofmann et. al, 1995). In addition, Dr. Whitney found similar results in her US wide study (Whitney et. al., 2008). Blacks were 1.6 times more likely to have a drug resistant strain of *S. pneumo* when compared to whites.

The age of a patient is the strongest predictor of DRSP and the rate of mortality is higher with extreme ages (Jenkins et. al., 2012, Lynch & Zhanel, 2010, Liu et. al., 2013). Pneumococcal disease is the leading cause of death in children under the age of five (Liu et. al., 2013). A study in China in a Pediatric Department of 61 patients under the age of five who were diagnosed with IPD was evaluated to understand serotyping and resistance patterns (Liu et. al., 2013). Out of 61 patients, 60% of the patients were under the age of two. The average hospital stay was 21 days and 20% of the patients were on a ventilator ranging from 1-39 days (Liu et. al., 2013). Among the cases under two years old, 13.5% of the cases died. The study demonstrated the burden of disease on such a young population and the high mortality rate among this group (Liu et. al., 2013). The researchers explain that an immature immunity in this age group increases their risk for infection and potential death (Liu et. al., 2013).

Although children have a high rate of mortality with DRSP, *S. pneumo* affects adults over the age of 65 in a similar way. Adults of a higher age have weakened immune systems and

potentially other health problems which can increase their likelihood of obtaining IPD (Jenkins et. al., 2012, Lynch & Zhanel, 2010). The mortality rate for older adults increases significantly when compared to children (Lynch & Zhanel, 2010). A study in Denmark of 18,000 IPD cases from 1977 – 2007 found the mortality rates for children under the age of 5 less than 3%; while the mortality among adults older than 65 was 24% (Denmark Study). Therefore, older adults with other comorbidities and children less than 5 years old are at the highest risk for DRSP (Jenkins et. al., 2012, Lynch & Zhanel, 2010).

Antibiotics Use and *Streptococcus pneumoniae*

The overuse of antibiotics has been associated with increasing rates of multidrug resistant *S. pneumo* (MRSP) (Cornick & Bentley, 2012, Richter, et. al., 2009, Mera et. al., 2004, Hicks et. al., 2011). Penicillin has been the standard of care for *S. pneumo* infections since its introduction in 1940 (Cornick & Bentley, 2012). However, due to the wide spread use of penicillin to battle these infections, the first penicillin resistant strain was discovered in the 1960s (Cornick & Bentley, 2012, Li et. al., 2011). Since then, other classes of antibiotics have been used in place of or in combination with penicillin such as macrolides and fluoroquinolones (Hicks et. al., 2011, Jenkins et. al., 2012). The increase in the number of antibiotics used to fight this infection has resulted in multidrug resistant *S. pneumo* becoming a major public health issue. A study conducted in 2004—2005 in the United States, found more than 20% of all pneumococcal isolates were resistant to penicillin and at least 2 other non β -Lactam drugs (Richter, et. al., 2009). In addition, the researchers found 32.5% of isolates were resistant to penicillin and 29.1% were resistant to erythromycin (Richter, et. al., 2009). The Alexander Project, a surveillance study from 1992-2001 of antibiotic resistant agents, found similar results (Mera et. al., 2004). In 1992, the percent of penicillin resistant isolates was 9.2%; while in 2001, it had increased to

20.1%. Likewise, erythromycin resistant isolates increased from 6.4% in 1992 and 28.3 in 2001 in the US and around the world (Mera et. al., 2004, Megged, Assous, Weinberg & Schlesinger, 2013). Previous studies have found recent antibiotic use as a risk factor for obtaining a strain of MRSP (Rivera & Boucher, 2011). Therefore since the emergence of penicillin resistance, the use of other antibiotics, such as erythromycin, has induced resistant strains of various other antibiotics.

β -Lactams are a class of antibiotics which include penicillin and amoxicillin. The class of antibiotics called macrolides, includes erythromycin and clindamycin (Stephens et. al., 2005). Fluoroquinolones include antibiotics such as lexofloxacin and cephalosporins include cefotaxime and ceftriaxone (Samore et al., 2006, Isea-Pena et. al., 2013). These various classes of antibiotics have increased in their prevalence of resistant strains due to overuse of penicillin (Samore et al., 2006). Dr. Samore and colleagues examined IPD cases in Utah and Idaho from 1998-2003 and found the majority of antibiotics being prescribed for IPD was penicillin/ β -Lactams (58%), cephalosporins (19%) and macrolides (19%) (2006). Dr. Samore found an association between cephalosporin use and penicillin resistance (2006). 15% of children who had penicillin resistant *S. pneumo* (PRSP), were administered a cephalosporin within the past 30 days in comparison to 7.5% of children who had penicillin (Samore et al., 2006).

Additionally, recent treatment with a cephalosporin, penicillin or macrolides promoted mechanisms by which they were more likely to have PRSP (Mera et. al., 2004, Samore et al., 2006). Fluoroquinolones are considered broad spectrum antibiotics and are typically administered to treat pneumonia in adults in combination with a β -lactam or alone when a patient is penicillin sensitive (Jenkins et. al., 2012, Isea-Pena et. al., 2013). The introduction of fluorquinolone use for *S. pneumo* infections is fairly recent, but fluoroquinolone resistance has

increased significantly due to increase of use (Jenkins et. al., 2008, Isea-Pena et. al., 2013).

Patients with Levofloxacin-resistant isolates are at a higher risk for mortality, septic shock and acute respiratory distress syndrome (Isea-Pena et. al., 2013). As a result, the increase in PRSP has pushed clinicians to find other alternatives for treatment such as combination therapy or broad spectrum antibiotics, which has indirectly increased the number of multi-drug resistant strains of *S. pneumo* and increased severity of illness.

The Effect of the Pneumococcal Conjugate Vaccine

While, antibiotics are useful to fight existing infections, there is controversy about long term antibiotic use and their effects on antibiotic resistance strains of *S. pneumo*. Therefore, prevention should be held a priority through proper hygiene and vaccination. Vaccines have been developed to target some of the most prolific polysaccharide serotypes that have been discovered to cause a majority of IPD cases. The most recent vaccine, PREVNAR 13, Pneumococcal 13-Valent Conjugate Vaccine (PCV13) was approved by the Federal Drug Administration (FDA) in February 2010 for use against invasive disease caused by *S. pneumo* (MMWR, 2013). This vaccine is recommended for ages 5-17 and 50 years of age and older (Wyeth Pharmaceuticals Inc., 2013). There are 13 serotypes the vaccine provides prevention against: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (Wyeth Pharmaceuticals Inc., 2013). The previous pneumococcal vaccine (PCV7) only covered seven serotypes.

Depending on the age and health of the patient, there are varying forms and doses of the pneumococcal vaccine that can be administered. Healthy children less than 2 years old should receive the PCV13 in four doses: 2 months, 4 months, 6 months, and 12 through 15 months (Centers for Disease Control and Prevention). All adults 19 years and older with the following

medical conditions and have not previously received PCV7 when they were younger, should receive PCV13 (CDC).

- Cerebrospinal fluid (CSF) leaks
- Cochlear implant(s)
- Sickle cell disease and other hemaglobinopathies
- Functional or anatomic asplenia
- Congenital or acquired immunodeficiencies
- HIV infection
- Chronic renal failure
- Nephrotic syndrome
- Leukemia
- Hodgkin disease
- Generalized malignancy
- Long-term immunosuppressive therapy
- Solid organ transplant
- Multiple myeloma

In addition to the PCV13 vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) includes 11 of the serotypes in the PCV13 with an additional 12 serotypes of protection (MMWR, 2013). Healthy adults age 65 and older should receive PPSV23 (CDC). Vaccine regimens can change based on age, missed vaccine dose and certain medical conditions. Patient should always seek their health care provider for the best course of treatment.

Table 2: Medical Conditions or Other Indicators for Administration of PCV13, and Indications for PPSV23 Administration and Revaccination for Children Aged 6-18 Years (CDC)

Risk group	Underlying medical condition	PCV13	PPSV23	
		Recommended	Recommended	Revaccination 5 yrs after first dose
Immunocompetent persons	Chronic heart disease [¶]		✓	
	Chronic lung disease ^{††}		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiencies ^{††}	✓	✓	✓
	Human immunodeficiency virus infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression ^{§§}	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

* 13-valent pneumococcal conjugate vaccine.

† 23-valent pneumococcal polysaccharide vaccine.

‡ Children aged 2–5 years with chronic conditions (e.g., heart disease or diabetes), immunocompromising conditions (e.g., human immunodeficiency virus), functional or anatomic asplenia (including sickle cell disease), cerebrospinal fluid leaks, or cochlear implants, and who have not previously received PCV13, have been recommended to receive PCV13 since 2010.

¶ Including congestive heart failure and cardiomyopathies.

** Including chronic obstructive pulmonary disease, emphysema, and asthma.

†† Includes B-(humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

§§ Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

The introduction of the PCV7 vaccine had dramatic results against IPD in the United States (Stephens et. al., 2005, Lynch & Zhanel, 2010, Cornick & Bentley, 2012, Wroe et. al., 2012). A prospective population-based surveillance study in Atlanta found IPD rates decreased after the introduction of the PCV7 vaccine in 2000 (Stephens et. al., 2005). The annual incidence of IPD from 1994-1999 was 30.2 and fell to 22.3 in 2001 and 13.1 in 2002 (Stephens et. al., 2005). The PCV7 was recommended for children ages 2-23 months and was given in 4 doses. Over three years, the Atlanta area saw an increase in the number of children participating in the vaccine with an average of 77-80% of children receiving at least 2 doses (Stephens et. al., 2005). The decrease in IPD was most drastic in children less than two with 82% decrease in cases from 1994-2002 (Stephens et. al., 2005). Although the vaccine was initially recommended for children, decreases of IPD cases in adults have been noted as well. The previous study reported a 39% decrease in adults 65 years and older (Stephens et. al., 2005). Researchers have stated this

observed decrease in adults is due to herd immunity (Lynch & Zhanel, 2010). The Centers for Disease Control explains herd immunity (or community immunity) as a situation when a majority of high risk individuals are immune to an infection, either by vaccination or prior illness, to prevent the spread of disease to others; therefore decreasing the incidence of disease in non-vaccinated individuals.

Although the PCV7 propagated a decrease in IPD cases after its introduction, a US wide study conducted by the Emerging Infectious Program noticed an increase in the number of IPD cases among children less than 5 in 2003. This increase corresponded with the rise of serotypes not included in PCV7 (Hampton et. al., 2011). Furthermore, the rates of PRSP increased as well in all age groups for serotypes not included in PCV7 (Hampton et. al., 2011). By 2007-2008, more than 70% of PRSP cases were caused by serotypes that are not included in PCV7 (Hampton et. al., 2011). Particularly, the increase of IPD cases was due to the serotype 19A (Cornick & Bentley, 2012). In the US, 19A is identified as the main cause of drug resistant IPD cases (Cornick & Bentley, 2012, Hampton et. al., 2011, Lynch & Zhanel, 2010). From 1998-2005, an increase of 6.7% - 35% was observed for penicillin resistant IPD cases caused by 19A (Cornick & Bentley, 2012).

A study conducted in Massachusetts examined the relationship between antibiotic resistant strains of pneumococcal disease after the introduction of PCV7 (Wroe et. al., 2012). Similar results were noticed; an initial decline in PCV7 serotypes, only to return to pre-PCV7 levels as a result of replacement by non-vaccine serotypes, particularly 19A (Wroe et. al., 2012). PCV13 was approved by the FDA in early 2010 for additional serotypes 1,3,5,6A, 7F and 19A (Wroe et. al., 2012). Little to no research has been conducted on the effects of PCV13 on penicillin resistant IPD cases and the population as a whole, however, researchers predict the

same scenario as PCV7 (Wroe et. al., 2012, Hampton et. al., 2011). Since PCV13 included 19A, initial decreases will occur, but potentially antibiotic pressure will drive emergence of new resistant serotypes (Cornick & Bentley, 2012, Wroe et. al., 2012).

Strategies for Battling Inadequate Antimicrobial Treatment

Previous research has associated frequent antibiotic use as a risk factor for acquiring a multidrug resistant *S. pneumo* (Mera et. al., 2004, Samore et al., 2006, Isea-Pena et. al., 2013). The Alexander Project, previously discussed, found similar results in their 10 year study (Mera et. al., 2004). Resistance to three or more antibiotics had increased from 0.8% in 1992 to 17.5% in 2001 (2004). Dr. Mera claims the most important factor influencing the increase of multidrug resistant *S. pneumo* is the inappropriate use of antibiotics (2004). Additionally, Dr. Timothy Jenkins conducted a study on prescribing practices of antibiotics for community acquired pneumonia based on the Infectious Disease Society of American (ISDA) guidelines (Jenkins et. al., 2012). The study examined whether doctors were following proper guidelines for patients who present with risk factors for acquiring PRSP such as recent antibiotic use, age and immunocompromised medical conditions (Jenkins et. al., 2012). Dr. Jenkins found only 9% of patients were treated with appropriate antibiotic therapy as prescribed by the ISDA guidelines (2012). Therefore, adherence to prescribing policies is low and could attribute to the emergence of multidrug resistant strains of *S. pneumo*.

Inadequate antimicrobial treatment can be defined as empirically treating infections without microbiological documentation of the organism and antibiotic susceptibility testing (Kollef, 2000). Also, not adhering to drug dosages or proper interval administration can also be included as inadequate antimicrobial treatment and can result in the development of antibiotic resistance (Kollef, 2000). Inadequate antimicrobial treatment has been associated with higher

mortality rates (Kollef, 2000). Researchers have suggested various strategies to reduce antibiotic resistance such as educating staff infectious disease specialists and uniform antibiotic prescribing guidelines (Kollef, 2000). The issue of *S. pneumo* infectious caused by the development of antibiotic resistant strains is due to various players and further research needs be examine to fully understand their relationship.

CHAPTER THREE: METHODS AND PROCEDURES

Study Population

Georgia is a participating site in the Active Bacterial Core Surveillance Program conducted through the Emerging Infections Program (EIP) at the Centers for Disease Control and Prevention (CDC). Confirmed cases of invasive *Streptococcus pneumoniae* are reported directly to the state through the State Electronic Notifiable Disease Surveillance System (SENDSS) within 7 days of disease onset by clinicians at local hospitals and laboratories. SENDSS is a passive reporting system and relies on hospitals and labs to report cases¹. Georgia is divided into two defined regions for the ABC Surveillance Program: Metro-Statistical Area (MSA) and Georgia Outer Areas (GOA). MSA includes the 20 counties surround the metro-Atlanta area² and GOA is the remaining 139 counties. Once cases are reported the state, medical chart reviews are conducted to answer extensive questions outlined by the EIP's Case Report Form. Available isolates from GOA are sent to Georgia State Public Health Laboratory and CDC for serotyping and antibiotic susceptibility testing. MSA isolates are processed at their lab and then sent to CDC for additional testing.

Data Collection

A process query was conducted from SENDSS to collect confirmed cases of invasive *S. pneumoniae* between 2009 and 2012. A confirmed case was defined as a patient with appropriate signs and symptoms of invasive *S. pneumo* infections, with isolation of *S. pneumo* from a normal sterile site such as blood, CSF or pleural fluid. The following variables were included in the query: patient ID, age, date of onset, gender, race, ethnicity, county of residence, region, diagnosis, hospital status, outcome and antibiotic susceptibility test results.

Antibiotic susceptibility results were collected for ten antibiotics: Penicillin, Amoxicillin, Erythromycin, Clindamycin, Cefotaxime, Trimethoprim, Tetracycline, Meropenem, Oxacillin and Levofloxacin. Minimum Inhibitory Concentrations were determined based on the Clinical and Laboratory Standards Institute, Seventieth Information Supplement (M100-S17). Intermediate and resistant results were grouped together as resistant.

Data Analysis

Data was analyzed using SAS software (v. 9.2). Cumulative incidence rates were calculated for each year based on the 2010 Census Bureau. Descriptive statistics were used to summarize risk factors and Pearson chi square test was calculated to test for trends and differences among the variables. Crude odds ratios were determined for each risk factor by penicillin resistant organisms. Variables were included in a final multivariate logistic regression model to control for each covariate. The model included penicillin resistant *S. pneumo* as the binary outcome variable and the demographic data (age, location, race, diagnosis, hospitalization) and antibiotic susceptibility testing results as the exposure variables³.

Antibiotic susceptibility results were imported into WHONET (v 5.6), a software program created by the World Health Organization to analyze antibiotic susceptibility results. Multidrug resistance profiles were examined using this software. Causal trends among antibiotics by penicillin resistance were determined through a Pearson Chi square test in SAS. For all analysis, p-value of <0.05 was considered statistically significant.

¹Antibiotic Susceptibility testing is only conducted for isolates sent from MSA. GOA isolates are done at the discretion of each individual hospital and is not required for every isolate. Some isolates for GOA are tested at the GPHL and CDC, but is not a requirement. MSA conducts active surveillance.

²Barrow, Bartow, Carroll, Cherokee, Clayton, Cobb, Coweta, Dekalb, Douglas, Fayette, Forsyth, Fulton, Gwinnett, Henry, Newton, Paulding, Pickens, Rockdale, Spalding, Walton, Clayton, Cobb, Dekalb, Douglas, Fulton, Gwinnett, Newton, Rockdale

³Multivariate Logistic Regression Model from Whitney 1998. Listed in References.

CHAPTER FOUR –RESULTS

Descriptive Statistics

A total of 5,040 cases of invasive *Streptococcus pneumoniae* were reported from 2009-2012 in Georgia. Seven of the cases originally reported lacked culture confirmation of *S. pneumo* and were not used in the final analysis. The total case count was 5033. Cumulative incidence rates based on population data from the 2010 Census Bureau are shown in Figure 1. Incidence and mortality rates increased with age, however the greatest disease burden was between ages 18-64 (Figure 2).

Figure 1: Cumulative Incidence Rates for Pneumococcal Isolates By Year

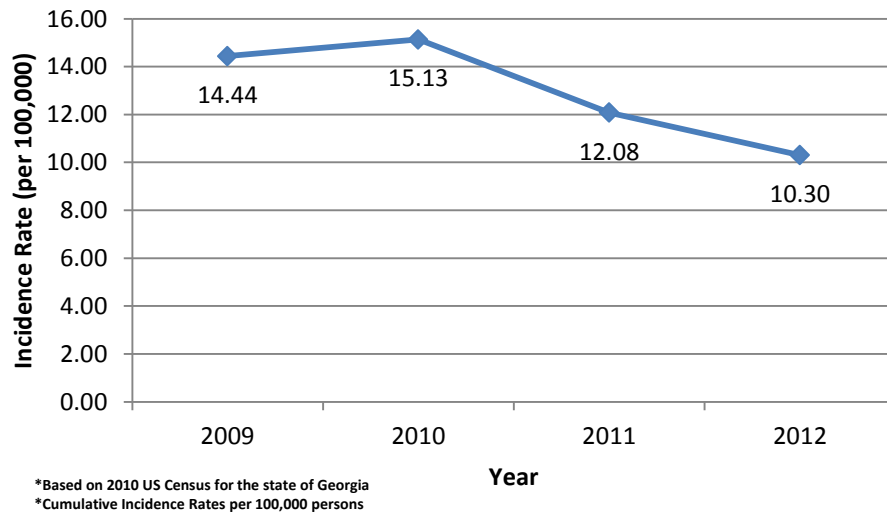
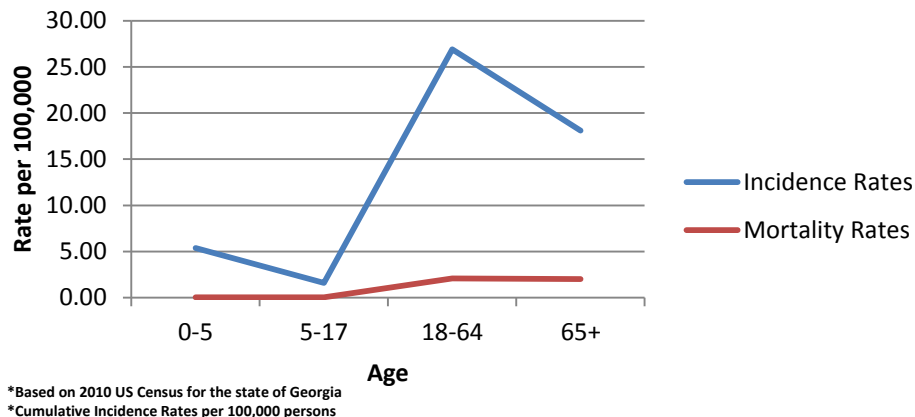
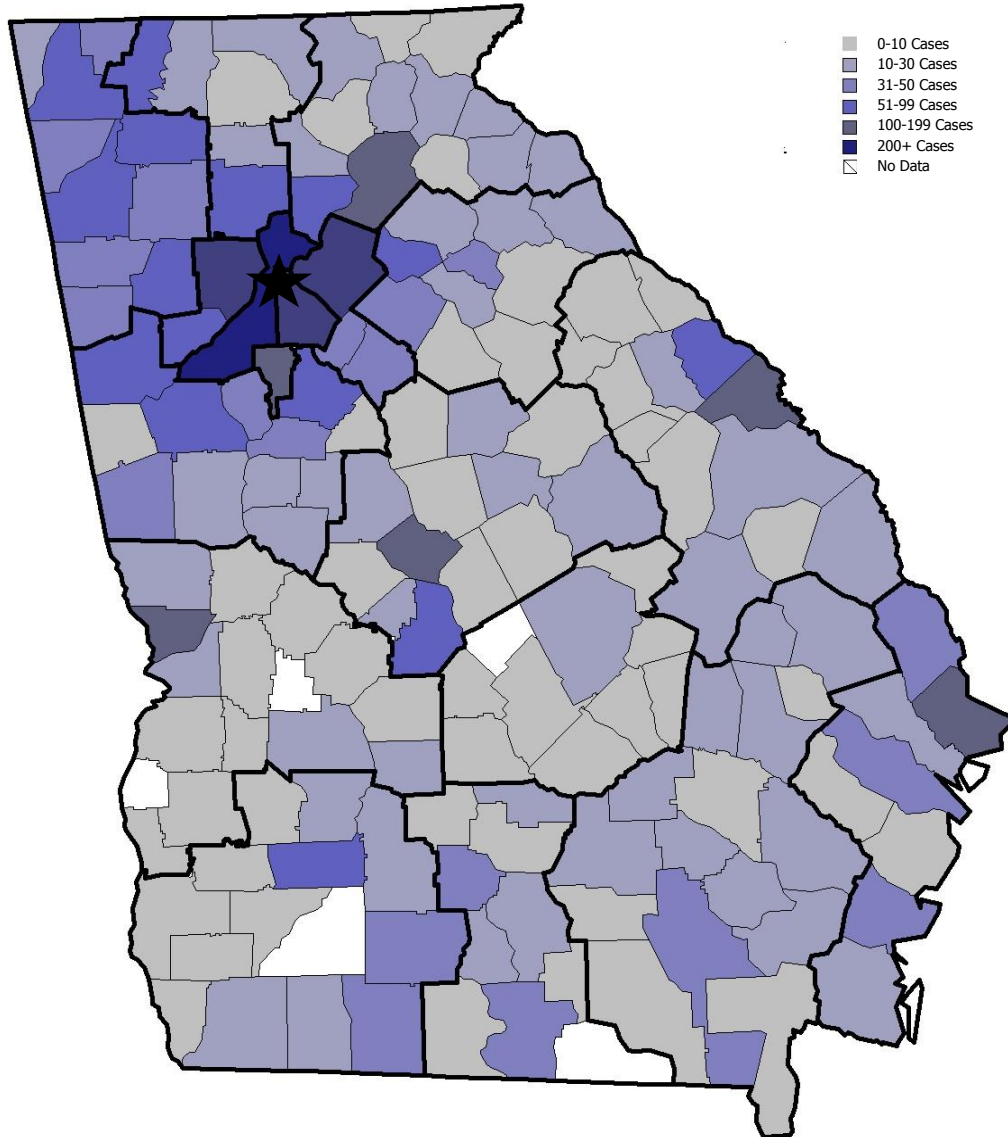


Figure 2: Incidence and Mortality Rates by Age



Of the 5,033 cases, 4,348 (86.39) patients were hospitalized because of their infection and 290 (5.76%) were not hospitalized. Hospitalization was defined as being admitted into the hospital for overnight stay, not including the emergency room. 55 cases did not have hospitalization information. Most cases were from the GOA region (2793, 55.49%) and 2240 (44.51%) cases were from the MSA. Based on the 2000 Census Bureau, 52.75% of the total population resides within MSA and the remaining 47.25% resides in GOA. The average age of the cases was 51.71. Most of the cases were 18-64 years of age (2606, 51.78%), 520 were less than 5 years of age (10.33%), 155 (3.08%) between the ages 5-17 and 1752 (34.81%) over the age of 65. The majority of cases were among whites (59.31%), 34.73% were among blacks and 5.96% were other or unknown. Spatial analysis on the distribution of cases demonstrated a large portion of cases in highly populated cities (Figure 3).

Figure 3: Spatial Distribution of Pneumococcal Isolates by Counties in Georgia
(star denotes MSA surrounding counties).



Patients were considered a case of meningitis if positive culture was isolated from the cerebral spinal fluid (CSF). 214 cases (5.3%) were culture confirmed with meningitis. Patients were diagnosed with pneumonia if a positive culture was isolated from the pleural fluid and 3003 (60.9%) were culture confirmed with pneumonia. Bacteremia was diagnosed if a positive culture

was isolated from a sterile site other than the CSF and pleural fluid and 724 (14.96%) cases were diagnosed with bacteremia. 1,095 cases have an unconfirmed diagnosis. For patients with unconfirmed diagnosis, a specific diagnosis was unable to be determined from medical chart reviews and is deemed “unconfirmed”. 4,375 (86.98) cases survived and 406 cases (8.07%) died from their illness. Outcome data for 249 cases (4.95%) is unknown.

Penicillin Resistant Streptococcus pneumoniae

2,917 (57.95%) of isolates were tested for penicillin susceptibility (Table 3). The number of penicillin-resistant *S. pneumo* (PRSP) was highest in GOA with 14.75% (OR 1.277). Among age groups, those children less than 5 had the highest number of PRSP with 16.34% of isolates (Figure 4). Adults older than 65 years (37.92%, OR 1.323) were also likely to have PRSP when compared to patients between the ages of 18-65. Blacks were more likely to have PRSP when compared to compared (OR 0.721, 15.10%). Due to missing values, statistical significance of PRSP could not be determined for diagnosis, hospitalization and outcome; however, over 60% of patients’ diagnosed pneumonia had PRSP (Figure 5).

Table 3: Multivariate Logistic Regression of Penicillin Resistance by Risk Factors¹

	Number of Isolates	% Resistant to Penicillin	Adjusted OR (95% CI)	P-value
Region				
MSA*	2240	12.05	1.00	
GOA	2793	14.75	1.277 (1.070-1.524)	0.0068
(MSA8)	1563	11.90		
Age				
<5 yrs	520	16.34	1.950 (1.453-2.613)	<.0001
5-17 yrs	155	9.68	0.642 (0.365-1.128)	0.1234
18-64 yrs*	2606	12.43	1.00	
>65 yrs	1752	14.78	1.323 (1.092-1.602)	0.0043
Race				
White	2985	12.6	0.721 (0.597-0.870)	0.0006
Black*	1748	15.10	1.00	
Other or Unknown	300	9.00	0.779 (0.508-1.193)	0.251
Hospitalized²				
Yes	4348	13.68	0.7739 (0.5456- 1.0977)	NS
No*	290	16.21	1.00	
Diagnosis³				
Meningitis	214	17.29	1.1195 (0.7598-1.6495)	NS
Pneumonia	3003	13.75	0.8723 (0.7031-1.0824)	NS
Bacteremia	724	13.95	1.2486 (0.9687-1.6095)	NS
Outcome⁴				
Survived*	4375	13.58	1.00	
Death	406	13.79	1.0235 (0.7481-1.4003)	NS

*Denotes reference category

¹The results are based on 2917 available isolates with penicillin susceptibility results.

²395 cases are missing hospitalization information. Statistical significant was unable to be determined based on missing data.

³1092 cases are missing diagnosis because of unconfirmed diagnosis. Statistical significant was unable to be determined based on missing data. Patients without listed diagnosis were the reference group.

⁴252 cases are missing outcome data. Statistical significant was unable to be determined based on missing data.

Figure 4: Percentage of Penicillin Resistant Pneumococcal Isolates by Age

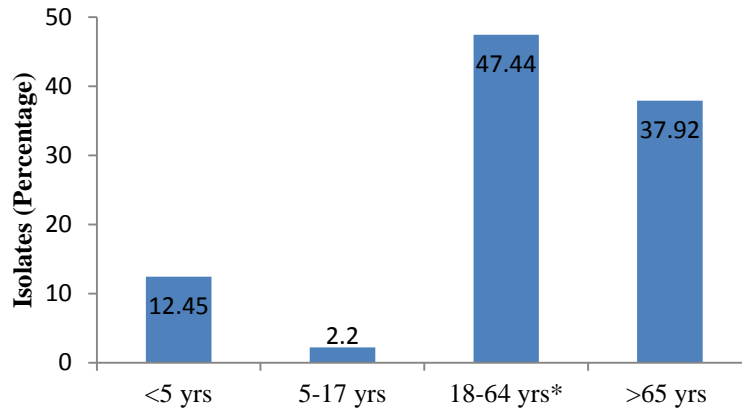
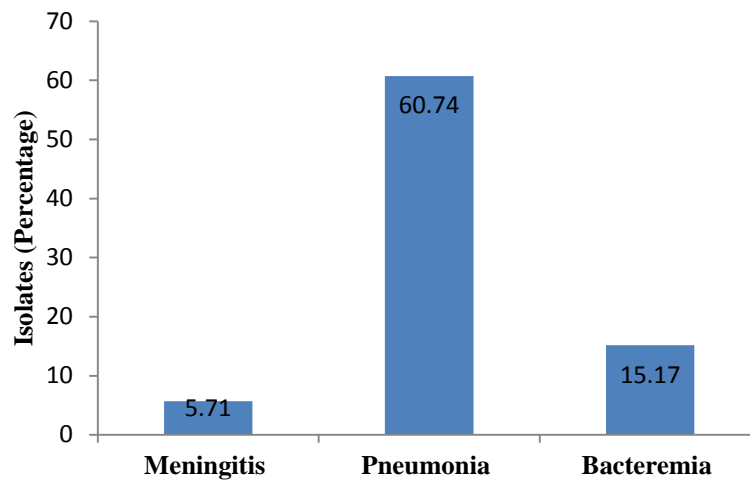
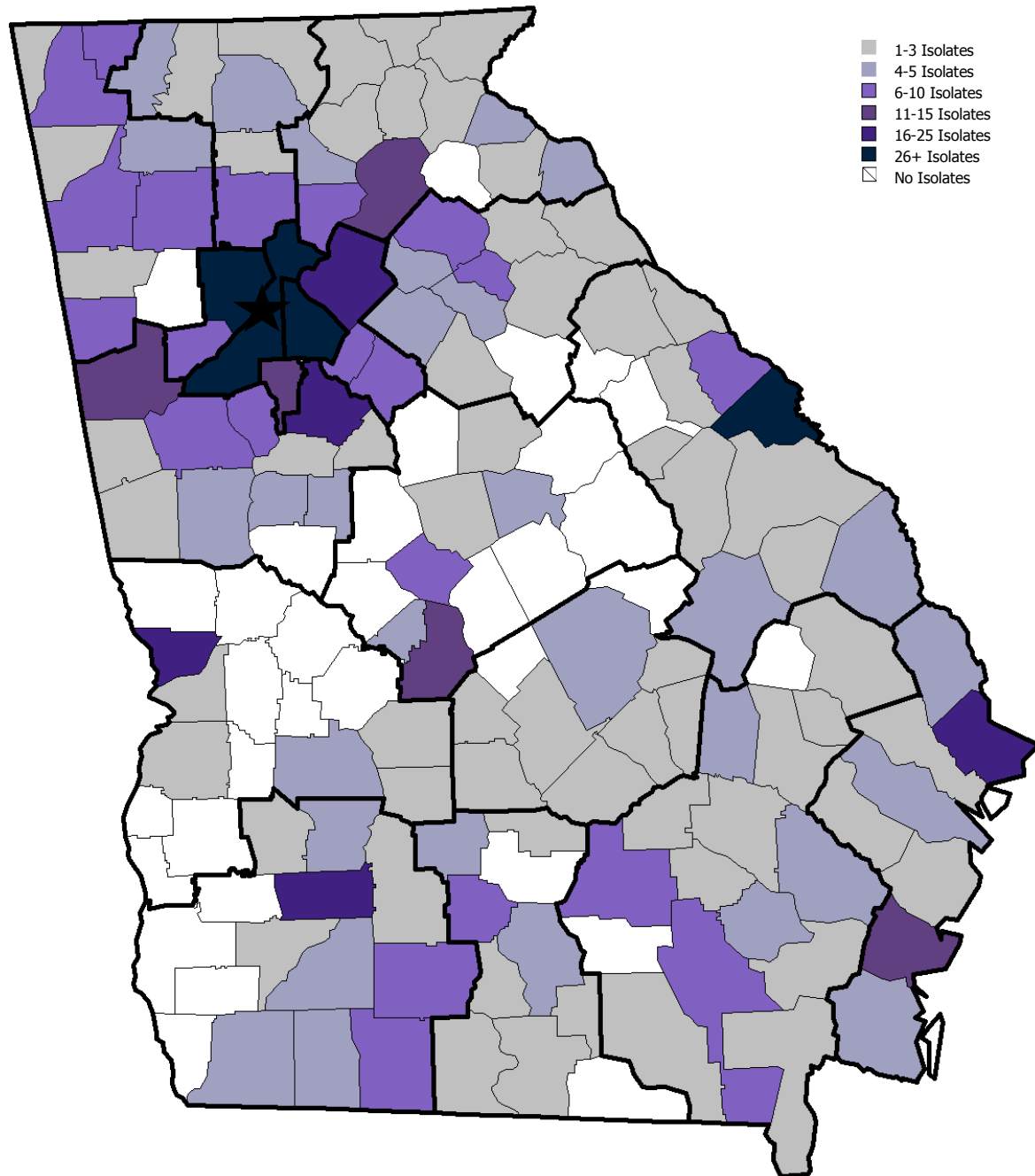


Figure 5: Percentage of Penicillin Resistance Pneumococcal Isolates by Primary Diagnosis



Spatial analysis of the distribution of penicillin resistant isolates compared to the overall case count showed some similarities (Figure 6). Most penicillin resistant isolates are located in highly populated counties, however clusters of high incidence of PRSP were found in southern counties with low population counts such as Dougherty, Glynn and Houston counties.

Figure 6: Spatial Distribution of Penicillin Resistant Pneumococcal Isolates by Counties in Georgia (N=683) (star denotes MSA surrounding counties)

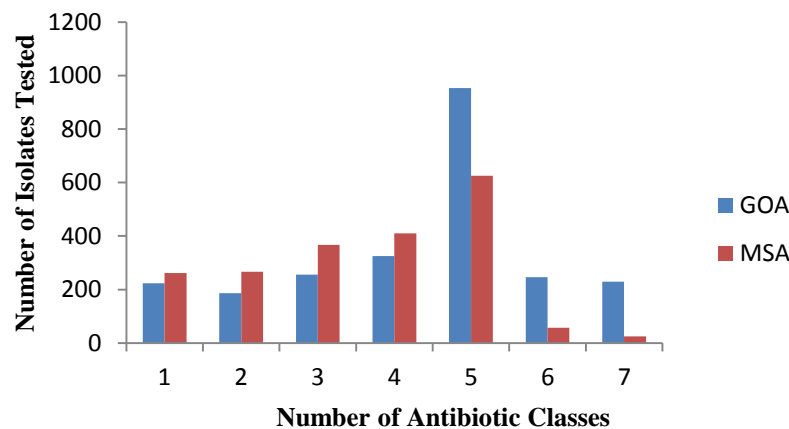


Multi-drug Resistant (MDR) Streptococcus pneumoniae

Multidrug resistant is defined as resistance to two or more antibiotics. Of all 5,033 isolates, 1,529 (34.5%) were resistant to at least one antibiotic. 603 isolates were excluded from

analysis because antibiotic susceptibility testing was unavailable or not tested. Depending on where antibiotic susceptibility testing was performed, every location has varying protocols on what classes of antibiotics are tested. Out of 7 classes of antibiotics, the average number of classes tested in GOA was 3.76 and MSA was 3.2. Typically, the MSA tested more classes of antibiotics compared to GOA (Figure 7). Since, labs and hospitals test a variety of combination of antibiotics, antibiotic susceptibility results are based on available data for each antibiotic. Amoxicillin, Oxacillin and Tetracycline were removed from the analysis because 50% of the cases were missing susceptibility results for these antibiotics. While these antibiotics are clinically relevant to *S. pneumo* infections, some hospitals and labs may not test for derivatives of penicillin like Oxacillin or Amoxicillin which would explain why so many isolates are missing these susceptibility results.

Figure 7: Number of Antibiotic Classes Tested for Each Isolate by Region



Resistance to a combination of any two antibiotics was most prevalent with 622 isolates (Figure 8). Penicillin resistance was associated with resistance to other antibiotics (Table 4). Resistant isolates of Erythromycin, Cefotaxime and Trimethoprim are the highest among

penicillin resistance. The highest number of MDR isolates was among 18-64 year olds with 276 isolates resistant to any combination of two antibiotics (Figure 8). Overall, the greatest proportion of MDR was among the older population (Figure 8). When analyzing resistant phenotypes, the most prevalent phenotypes were Cefotaxime and Erythromycin with 517 (10.27%) isolates and the combination of Cefotaxime, Erythromycin and Penicillin with 277 (5.5%) isolates (Table 5).

Figure 8: Number of Multi-Drug Resistant Pneumococcal Isolates by Age

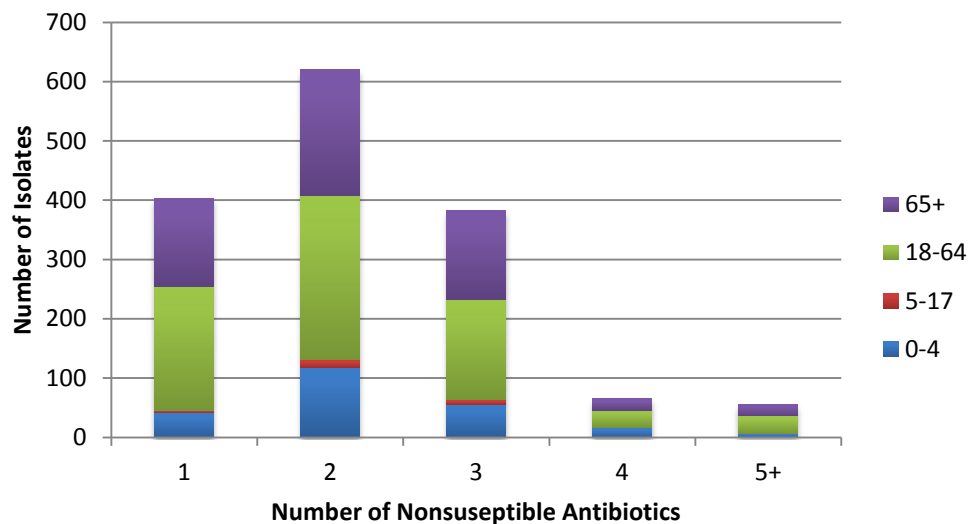


Table 4: Percentage of Resistant Isolates to Each Antibiotic based on Penicillin Resistance

	<i>Susceptible to Penicillin (%)</i>	<i>Resistant to Penicillin (%)</i>	<i>P-Value</i>
Erythromycin	10.8	17.43	<.0001
Clindamycin	0.67	0.62	0.0082
Meropenem	4.14	15.09	<.0001
Cefotaxime	12.56	16.67	<.0001
Lexofloxacin	0.8	0.8	0.001
Trimethoprim	6.3	16.26	<.0001
Levofloxacin	0.8	0.8	<.0001

Table 5: Resistant Phenotypes by Number of Resistant Antibiotics

# of Resistant Isolates	Resistance Phenotype	N (%)
1	CTX	72 (1.4)
1	ERY	25 (.49)
1	MEM	15 (0.30)
1	PEN	248 (4.9)
1	TCY	39 (0.77)
2	CLI LVX	15 (0.30)
2	CTX ERY	517 (10.27)
2	CTX PEN	26 (0.51)
2	CTX TCY	9 (0.18)
2	PEN ERY	22 (0.44)
2	PEN MEM	8 (0.16)
2	PEN TCY	10 (0.20)
3	CTX ERY MEM	15 (0.30)
3	CTX ERY PEN	277 (5.5)
3	CTX ERY TCY	47 (0.93)
3	CTX PEN TCY	7 (0.14)
4	AMX CTX ERY CLI	13 (0.26)
4	CTX ERY CLI LVX	7 (0.14)
4	CTX TCY PEN ERY	8 (.016)
4	CTX TCY PEN MEM	5(0.10)
5	AMX CTX CLI ERY MEM	2 (0.04)
5	AMX CTX CLI ERY PEN	1 (0.02)
5	AMX CTX CLI ERY TCY	8 (0.16)
5	CTX CLI MEM PEN TCY	10 (0.2)
6	AMX CTX CLI ERY MEM TCY	9 (0.18)
6	AMX CTX CLI ERY PEN LVX	2 (0.04)
6	AMX CTX CLI ERY PEN TCY	7 (0.14)
7	AMX CTX CLI ERY MEM TCY LVX	1 (0.02)
7	AMX CTX CLI ERY MEM TCY PEN	3 (0.06)
8	AMX CTX CLI ERY LVX MEM PEN TCY	1 (0.02)

CHAPTER V – DISCUSSION AND CONCLUSIONS

The overall incidence and mortality rates of *S. pneumo* have declined since 1998. The initiation of vaccination with PVC13 in 2010 is one of the potential contributing factors to a decline in incidence from 2010 to 2012 (Figure 1). Based on age, the heaviest burden of disease is among the 18-64 years olds which encompass over half of all the cases in Georgia. The pneumococcal vaccines have propagated change among incidence rates in children less than 5 and adults older than 65 years. In previous years, children and older adults were the age groups with the highest risk of severe illness and mortality from *S. pneumo* infections. Figure 2 emphasizes the change in incidence and mortality rates based on age. Because pneumococcal vaccines and intervention programs have targeted children, mortality has become nearly non-existent in this age group. Although the incidence rates have decrease for adults over 65 years old, mortality rates remain the same (Figure 2). This could be due to long term chronic health disorders that weaken their immune system and are unable to fight *S. pneumo* infections. Although the PCV13 and PPSV23 target adults with chronic health disorders, further intervention and educational programs through primary care physicians could increase the number of older adults receiving the vaccine and decrease mortality rates among this group.

The number of cases among middle age adults (18-64), for which no vaccine is recommended for healthy individuals, is notable. In 1998, Dr. Whitney's study found a large proportion of the cases within this age group as well (42.04%) and 19.3% of the isolates among this age group were penicillin resistant (Whitney et al). Dr. Whitney's percentages are based on national data from eight states included Georgia. Today in Georgia, 52% of the cases fall into this age group (18-64) and 12.43% of all isolates were penicillin resistant within the whole state of Georgia (Table 3). However, in 1998 when Dr. Whitney conducted her study, 33.2% of all

isolates in Georgia were penicillin resistant. Today, penicillin resistance within the eight counties used in Dr. Whitney's study is 11.9%. Therefore, there continues to be an increase in the number of cases of invasive *S. pneumo*, but a decline in penicillin resistance. However, no intervention programs are targeted for this age group. PCV13 and PPSV23 are recommended for this age group, if, they engaged in certain risky behaviors such as smoking or have immunocompromising medical conditions. Previous studies have attributed herd immunity for the decrease in the number of cases among non-vaccinated age groups such as this; however, the burden of disease continues to increase within these individuals.

This study is among the first to analyze *S. pneumo* cases within the entire state of Georgia. Heavily populated counties such as Fulton, Dekalb, Cobb, Bibb Richmond and Chatham counties have higher number of cases. However, if you compare the spatial analysis of penicillin resistant pneumococcal isolates across the state, you continue to see the same pattern except for clusters of high level of penicillin resistant isolates in various southern counties such as Dougherty and Houston (Figure 6). There are limited cases of PRSP in central Georgia and most of the cases reside in Northern and Southern parts of the state. Further analysis of the various clusters of PRSP show they are located in highly populated cities such as Albany, Columbus and Brunswick with large hospitals that would attract individuals from counties without a major hospital. This could increase in the number of cases reported in these counties.

Penicillin resistant strains of *S. pneumo* have decreased from previous research (Whitney et al, 2008; Mera et. al, 2005; Draghi et, al., 2006; Hofmann et. al., 1995). However, the emergence of resistant erythromycin and cefotaxime is becoming a major public health concern. Selective pressure is pushing resistance to these antibiotics from the long term over use of penicillin (Cornick & Bentley, 2012; Wroe et. al., 2012). The emergence of more antibiotic

resistance strains of the *S. pneumo* increases the severity of the illness and cost of treatment. This decreases the quality of life for the individual and increases the financial burden on the hospital. Although is it not statistically significant, it is important to note that 17% of all meningitis cases were penicillin resistant strains. Because meningitis is a time-sensitive and severe illness, physicians are potentially more likely to empirically treat such infections without proper antimicrobial testing. The recommended treatment for pneumococcal meningitis is penicillin and among penicillin resistant individuals, cefotaxime. Penicillin has been treating patients for various illnesses for over 30 years and the consistent use of this antibiotic for more than just *S. pneumo* infections and improper use has increased the burden of resistance strains. Therefore empirical treatments and over use of antibiotics are pushing emergence of resistant strains (Cornick & Bentley, 2012; Wroe et. al., 2012). Public health officials need to be cognizant of this issue and push for better surveillance to protect the health of Georgia.

The highest number of multidrug resistant strains was in adults over 18 years old. Nearly 75% of all multidrug resistant cases fall into this category (Figure 8). Figure 7 describes the number of classes tested by each region. Overall, MSA tests more classes of antibiotics compared to GOA. Currently, no standard exists for hospitals and laboratories on the number of classes tested during antibiotic susceptibility testing. This explains the discrepancies between testing practices of GOA and MSA. The hospital demographics within the MSA can explain the differences in testing practices. The MSA contains most of the major hospitals located in the state and therefore, potentially more funding and higher budgeting for more antibiotic susceptibility. GOA, on the other hand, contains many of the suburban counties with smaller hospitals and less budgeting and resources for antibiotic susceptibility testing. Georgia would benefit from a standardized antibiotic susceptibility protocol initiated statewide in order to

understand the full effect of DRSP on the state. Without a standardized antibiotic susceptibility results, it is difficult to analyze and make definitive assumptions and effective recommendations with missing data.

Limitations

There are several limitations constraining the results of this study. The MSA conducts active isolate surveillance, with GOA conducts passive isolate surveillance. The MSA routinely contacts hospitals and labs on a weekly basis to find cases and also has direct access to some hospital systems data. Some active surveillance is conducted by surveillance officers on a monthly basis, but not as frequent as MSA. Passive surveillance could result in under-reporting among GOA residents, hospitals and laboratories. Also, in order to completely fill out the case report form, the ABCs epidemiologist relies solely on the local hospitals to send medical charts for the patients to gather additional medical information. However, some hospitals do not send the entire chart and information is missing on the case report form. The result is missing data for variables such as diagnosis, hospitalization and outcome. In addition, there is not a minimum standard number of antibiotic classes tested at each hospital or lab for susceptibility testing. Each location determines what susceptibility tests are performed and how many classes are tested. As a result, antibiotic susceptibility results are variable and missing data is high among this group. The results from the study are solely from the state of Georgia and might not be generalizable to other populations with varying demographic distributions.

Recommendations and Future Studies

Therefore, based on the results of this study, a standardized protocol for antibiotic susceptibility testing would be beneficial to include in antibiotic stewardship programs statewide.

Uniform antibiotic testing results would provide the state a stronger surveillance of antibiotic resistance strains and understand the full nature of the issue. The multitude of missing data within the state's surveillance systems leaves questions unanswered about the true public health issue of antibiotic resistant strains of *S. pneumo* in Georgia. Over time, this data would be valuable to piloting future programs and interventions towards targeted resistant strains and at risk individuals.

The ACIP guidelines recommends vaccination of adults ages 18-64 only if they have certain immunocompromising medical conditions or engage in high risk behaviors such as smoking. However, the results from this study demonstrate the burden of disease lies heavy with this age group but interventions remain targeted towards young children and older adults. A future study should include looking at the relationship between *S. pneumo* infections in adults, aged 18-64, with immunocompromising medical conditions as outlined by the ACIP guidelines. This would demonstrate whether current guidelines are appropriate to only recommend vaccination to these specific individuals or whether many of these individuals with *S. pneumo* are relatively healthy without various medical conditions. If many of the individuals do not have immunocompromising medical conditions, then re-evaluating the guidelines in this age group would be beneficial to preventing future infections and mortality.

Also, future studies on this age group should be focused around vaccination and increasing education to providers about vaccination. Previous studies on vaccination rates among individuals in this age group have demonstrated that pneumococcal vaccinations among immunocompromised individuals are typically low (Greby et. al., 2010). Future studies should target programs to increase vaccination rates among these individuals to lower the incidence of pneumococcal disease. In addition, programs should target primary care physicians on increasing

education about pneumococcal vaccinations and encouraging their patients to become vaccinated who present with signs of immunocompromising medical conditions as outlined by the ACIP guidelines.

Currently, MSA is the only EIP region in Georgia where serotyping to the specific *S. pneumo* strain is available. Due to funding, and the relatively new addition of GOA to EIP, GOA does not perform serotype testing. All of the previous studies conducted in Georgia with *S. pneumo* serotype information have come from the 20 metro Atlanta counties in MSA. In order to better understand the relationship between the newest pneumococcal vaccine and *S. pneumo*, serotyping in GOA needs be incorporated into the laboratory testing and surveillance of *S. pneumo*. Because of the overuse of antibiotics in Georgia and the use of vaccines, selective pressure for new virulent strains is possible and needs to be monitored. Serotyping will allow epidemiologist to evaluate the current strains that are dominating in Georgia, which strains are more likely to be drug resistant and whether new strains are evolving for which the vaccine provides no protection.

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